FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.5)
PG3733USW	10/018640

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB00/02516	June 30, 2000	July 1, 1999

TITLE OF INVENTION
NEW USES FOR POTASSIUM CHANNEL OPENERS

APPLICANT(S) FOR DO/EO/US
Stephen Anthony Burbidge, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

PCT Request
PCT Coverpage of Publication

Express Mail No:
EL395889790US

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/018640	PCT/GB00/02516	PG3733USW

24. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	$1040.00
☒	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	$890.00
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$740.00
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$710.00
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	$100.00

ENTER APPROPRIATE BASIC FEE AMOUNT = $890.00

Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)). $0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	8 - 20 =	0	x $18.00	$0.00
Independent claims	8 - 3 =	5	x $84.00	$420.00
Multiple Dependent Claims **(check if applicable)**.			☐	$0.00

TOTAL OF ABOVE CALCULATIONS = $1,310.00

☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2. $0.00

SUBTOTAL = $1,310.00

Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). + $0.00

TOTAL NATIONAL FEE = $1,310.00

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐ $0.00

TOTAL FEES ENCLOSED = $1,310.00

Amount to be: refunded $

charged $

a. ☐ A check in the amount of _____ to cover the above fees is enclosed.

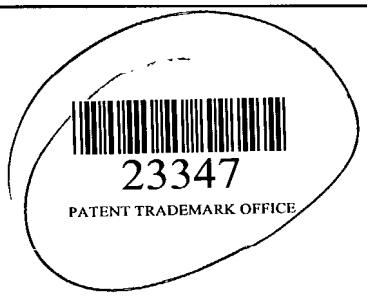
b. ☒ Please charge my Deposit Account No. **07-1392** in the amount of **$1,310.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **07-1392** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:



Bonnie L. Deppenbrock
SIGNATURE

Bonnie L. Deppenbrock
NAME

28,209
REGISTRATION NUMBER

12/18/01
DATE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Stephen Anthony Burbidge, et al.
International Application No.:	PCT/GB00/02516
International Filing Date:	June 30, 2000
Title:	NEW USES FOR POTASSIUM CHANNEL OPENERS

Assistant Commissioner for Patents
Washington, D.C. 20231

Attention: Box PCT/DO/EO/US

FIRST PRELIMINARY AMENDMENT

Sir:

The above identified application is being transmitted herewith for entry into the U.S. National Phase under Chapter II of the PCT. For the purposes of adding the priority information, please amend the application as follows:

In the Abstract:

Please substitute the attached Abstract, which has been placed on a separate piece of paper according to US practice.

In the Specification:

On the first line of the specification, after the Title, please add:

--This application is filed pursuant to 35 U.S.C. § 371 as a United States National Phase Application of International Application No. PCT/GB00/02516 filed June 30, 2000, which claims priority from 9915414.8 filed July 1, 1999 --

In the Claims:

Please amend the claims as follows:

Cancel Claims 1 through 2, 4 through 6 and 8.

In lieu therefor, please add the following new claims:

--9. A method for preparing a medicament for use as an anti-eplileptic comprising using a KCNQ2/3 potassium channel opener.--

Express Mail No:
EL395889790US

--10. A method for the preparation of a medicament for use as a muscle relaxant, fever reducer, or anxiolytic; use in migraine, bipolar disorder, unipolar depression, functional bowel disorders, or tinnitus; use in preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence-inducing agent; use in cancerous diseases, inflammatory processes, or opthalmic diseases; and use as an analgesic comprising using a KCNQ2/3 potassium channel opener.--

--11. A method for producing a muscle relaxant, fever reducer, or anxiolytic; for treating migraine, bipolar disorder, unipolar depression, functional bowel disorders, or tinnitus; for preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence-inducing agent; for treating cancerous diseases, inflammatory processes, or opthalmic diseases; or for producing an analgesic effect; in a mammal, including man, comprising administration of an effective amount of a KCNQ2/3 potassium channel opener.--

--12. A method for the preparation of a medicament for the treatment of conditions ameliorated by KCNQ2/3 potassium channel opening comprising using retigabine.--

--13. A method for the preparation of a medicament for use in neurotransmission disorders; CNS disorders; functional bowel disorders; neurodegenerative diseases; neuroprotection; tinnitus; preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence – inducing agent; cancerous diseases; inflammatory processes; opthalmic diseases; cognitive disorders; and migraine; and or as a centrally acting analgesic comprising using retigabine.--

--14. A mothod for the treatment of neurotransmission disorders, CNS disorders, functional bowel disorders, neurodegenerative diseases, or tinnitus; preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence – inducing agent; the treatment of cancerous diseases, inflammatory processes, opthalmic diseases, cognitive disorders, or migraine; and producing a neuroprotecting, or a centrally acting analgesic effect; in a mammal, including man, comprising administration of an effective amount of retigabine.--

PG3733USW

REMARKS

Claims 1-2, 4-6 and 8 have been canceled by this amendment. Currently claims 3, 7, and 9-14 are pending in the application. The subject matter of Claims 1-2, 4-6 and 8 have been cancelled and rewritten as new Claims 9-14 in a format more acceptable to the Patent Office. Hence, there is no new matter. Applicants have attached an abstract on a separate sheet of paper as required by US practice. Applicants have amended the specification for purposes of adding the priority information.

Respectfully submitted,

Bonnie L. Deppenbrock
Attorney for Applicants
Registration No.28,209

Date: 12/18/01

GlaxoSmithKline
Corporate Intellectual Property
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709
Phone: 919-483-1577
Facsimile: 919-483-7988

ABSTRACT

NEW USES FOR POTASSIUM CHANNEL OPENERS

The present invention relates to novel uses for retigabine and KCNQ2/3 potassium channel openers.

NEW USES FOR POTASSIUM CHANNEL OPENERS

The present invention relates to new uses for the compound retigabine and new uses for KCNQ2/3 potassium channel openers.

Retigabine, 2-amino-4-(4-fluorobenzylamino)-1-ethoxycarbonylaminobenzene, is a known anti-convulsant compound described for example in US5,384,330. The mechanism of action of retigabine is not known, but there are reports of activity against a potassium channel expressed in PC12 and NG108-15 cells. Retigabine has also been reported to increase *de novo* GABA synthesis in neurones and act at piperidic acid A receptors.

It has now been found that retigabine is a KCNQ2/3 potassium channel opener and retigabine's anti-convulsant activity is due to its activity at these channels.

KCNQ2 and KCNQ3 together form a heterotetrameric nervous system-specific potassium channel described for example in WO99/07832. WO99/07832 suggests utilities for modifiers of KCNQ2/3 channels including neurotransmission, ataxia, myokymia, seizures (e.g. epileptic seizures), Alzheimer's disease, Parkinson's disease, age-associated memory loss, learning deficiencies, motor neuron diseases and stroke. However, there is no teaching as to whether KCNQ2/3 openers or closers would be of use in the above diseases and no *in vitro* or *in vivo* support for these suggestions. WO99/07832 does not disclose any compounds active at KCNQ2/3 receptors. Linopirdine is a known compound which is a selective KCNQ2/3 blocker with cognition enhancing activity.

It has now been found that KCNQ2/3 potassium channel openers are useful as, amongst others, analgesics, fever reducers, muscle relaxants, anxiolytics and are of use in migraine, bipolar disorder and unipolar depression.

The invention accordingly provides, in a first aspect, the novel use of retigabine as a KCNQ2/3 potassium channel opener.

There is also provided as a further aspect of the invention the use of retigabine in the preparation of a medicament for use in the treatment of conditions ameliorated by KCNQ2/3 potassium channel opening.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, suffering from or susceptible to conditions ameliorated by KCNQ2/3 potassium channel opening, comprising administration of an effective amount of retigabine.

In a further aspect there is provided the use of retigabine in the preparation of a medicament for: use in neurotransmission disorders; CNS disorders; functional bowel disorders; neurodegenerative diseases; neuroprotection; tinnitus; preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence - inducing agent; cancerous diseases; inflammatory processes; ophthalmic diseases; cognitive disorders; and migraine; and use especially as a centrally acting analgesic.

In a yet further aspect the invention provides a method for: the treatment of neurotransmission disorders, CNS disorders, functional bowel disorders, neurodegenerative diseases, or tinnitus; preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence - inducing agent; the treatment of cancerous diseases, inflammatory processes, ophthalmic diseases, cognitive disorders, or migraine; and producing a neuroprotecting, or more especially a centrally acting analgesic effect; in a mammal, including man, comprising administration of an effective amount of retigabine.

In a further aspect the invention provides the use of a KCNQ2/3 potassium channel opener in the preparation of a medicament for: use as a muscle relaxant, fever reducer, or anxiolytic; use in migraine, bipolar disorder, unipolar depression, functional bowel disorders, or tinnitus; use in preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence - inducing agent; use in cancerous diseases, inflammatory processes, or ophthalmic diseases; and use especially as an analgesic.

In a further aspect the invention provides a method: of producing a muscle relaxant, fever reducing, or anxiolytic effect; for treating migraine, bipolar disorder, unipolar depression, functional bowel disorders, or tinnitus; for preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence - inducing agent; for treating cancerous diseases, inflammatory processes, or ophthalmic diseases; and especially of producing an analgesic effect; in a mammal, including man, comprising administration of an effective amount of a KCNQ2/3 potassium channel opener.

In a further aspect the invention provides the use of a KCNQ2/3 potassium channel opener in the preparation of a medicament for use as an anti-epileptic.

In a further aspect the invention provides a method for the treatment of a mammal, including man, suffering from or susceptible to epilepsy, comprising administration of an effective amount of a KCNQ2/3 potassium channel opener.

According to the instant invention KCNQ2/3 potassium channel openers including retigabine are useful as anticonvulsants. They are therefore useful in treating epilepsy. They may be used to improve the condition of a host, typically a human being, suffering from epilepsy. They may be employed to alleviate the symptoms of epilepsy in a host. "Epilepsy" is intended to include the following seizures:- simple partial seizures, complex partial seizures, secondary generalised seizures, generalised seizures including absence seizures, myoclonic seizures, clonic seizures, tonic seizures, tonic clonic seizures and atonic seizures.

KCNQ2/3 potassium channel openers including retigabine are additionally useful in the treatment of CNS disorders such as bipolar disorder, alternatively known as manic depression. Type I or II bipolar disorder may be treated. The compounds may thus be used to improve the condition of a human patient suffering from bipolar disorder. They may be used to alleviate the symptoms

of bipolar disorder in a host. The compounds may also be used in the treatment of unipolar depression, ataxia, myokimia and anxiety.

KCNQ2/3 potassium channel openers including retigabine are also useful as analgesics. They are therefore useful in treating or preventing pain. They may be used to improve the condition of a host, typically a human being, suffering from pain. They may be employed to alleviate pain in a host. Thus, the compounds may be used as a pre-emptive analgesic to treat acute pain such as musculoskeletal pain, post operative pain and surgical pain, chronic pain such as chronic inflammatory pain (e.g. rheumatoid arthritis and osteoarthritis), neuropathic pain (e.g. post herpetic neuralgia, trigeminal neuralgia and sympathetically maintained pain) and pain associated with cancer and fibromyalgia. The compounds may also be used in the treatment or prevention of pain associated with migraine. The compounds may also be used in the treatment of the pain (both chronic and acute), fever and inflammation of conditions such as rheumatic fever; symptoms associated with influenza or other viral infections, such as the common cold; lower back and neck pain; headache; toothache; sprains and strains; myositis; neuralgia; synovitis; arthritis, including rheumatoid arthritis; degenerative joint diseases, including osteoarthritis; gout and ankylosing spondylitis; tendinitis; bursitis; skin related conditions, such as psoriasis, eczema, burns and dermatitis; injuries, such as sports injuries and those arising from surgical and dental procedures.

KCNQ2/3 potassium channel openers including retigabine are further useful in the treatment of functional bowel disorders which include non-ulcer dyspepsia, non-cardiac chest pain and in particular irritable bowel syndrome. Irritable bowel syndrome is a gastrointestinal disorder characterised by the presence of abdominal pain and altered bowel habits without any evidence of organic disease. The compounds may thus be used to alleviate pain associated with irritable bowel syndrome. The condition of a human patient suffering from irritable bowel syndrome may thus be improved.

KCNQ2/3 potassium channel openers including retigabine are also useful in the treatment of neurodegenerative diseases, such as Alzheimer's disease,

ALS, motor neuron disease, Parkinson's disease, macular degeneration and glaucoma. The compounds may also be useful in neuroprotection and in the treatment of neurodegeneration following stroke, cardiac arrest, pulmonary bypass, traumatic brain injury, spinal cord injury or the like.

KCNQ2/3 potassium channel openers including retigabine are further useful in the treatment of tinnitus.

KCNQ2/3 potassium channel openers including retigabine are additionally useful in the treatment of migraine.

Still further, KCNQ2/3 potassium channel openers including retigabine are also useful in preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence - inducing agent. Examples of dependence inducing agents include opioids (e.g. morphine), CNS depressants (e.g. ethanol), psychostimulants (e.g. cocaine) and nicotine.

KCNQ2/3 potassium channel openers including retigabine may inhibit cellular and neoplastic transformation and metastatic tumour growth and hence be useful in the treatment of certain cancerous diseases, such as colonic cancer.

KCNQ2/3 potassium channel openers including retigabine may inhibit inflammatory processes and therefore may be of use in the treatment of asthma, allergic rhinitis and respiratory distress syndrome; gastrointestinal conditions such as inflammatory bowel disease, Chron's disease, gastritis, irritable bowel syndrome and ulcerative colitis; and the inflammation in such diseases as vascular disease, migraine, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, type I diabetes, myasthenia gravis, multiple sclerosis, sorcoidosis, nephrotic syndrome, Bechet's syndrome, polymyositis, gingivitis, conjunctivitis and myocardial ischemia.

KCNQ2/3 potassium channel openers including retigabine may also be useful in the treatment of ophthalmic diseases such as retinitis, retinopathies, uveitis and of acute injury to the eye tissue.

KCNQ2/3 potassium channel openers including retigabine may also be useful for the treatment of cognitive disorders such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease and Creutzfeldt-Jakob disease), and vascular dementia (including multi-infarct dementia), as well as dementia associated with intracranial space occupying lesions, trauma, infections and related conditions (including HIV infection), metabolism, toxins, anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Loss; and learning deficiencies.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms.

The KCNQ2/3 potassium channel opening activity of retigabine has been illustrated by the following method.

Expression of KCNQ2 & KCNQ3 in *Xenopus* oocytes: Modulation by Retigabine.

Human KCNQ2 and KCNQ3 potassium channels were cloned from a human brain CDNA library using standard methodology. All clones were sequenced and were identical to those reported in the literature (Charlier, C., Singh, N.A., Ryan, S.G., Lewis, T.B., Reus, B. E., Leach, R.J. Leppert, M. (1998). A pore mutation in a novel KQT-like potassium channel gene in an idiopathic epilepsy family. *Nature Genetics* **18**: 53-55 and Singh, N.A., Charlier, C., Stauffer, D., DuPont, B.R., Leach, R.J., Melis, R., Ronen, G.M., Bjerre, I., Quattlebaum, T., Murphy, J.V., McHarg, M.L., Gagnon, D., Rosales, T.O., Peiffer, A., Anderson, E & Leppert, M. (1998*) Nature Genetics,* **18**: 25-29).

Adult female *Xenopus laevis* (Blades Biologicals) were anaesthetised using 0.2% tricaine (3-aminobenzoic acid ethyl ester), killed and the ovaries rapidly removed. Oocytes were de-folliculated by collagenase digestion (Sigma type I, 1.5 mg ml^{-1}) in divalent cation-free OR2 solution (82.5mM NaCl, 2.5mM KCl, 1.2mM NaH_2PO_4, 5mM HEPES; pH 7.5 at 25°C). Single stage V and VI oocytes were transferred to ND96 solution (96mM NaCl, 2mM KCl, 1mM

$MgCl_2$, 1.8mM $CaCl_2$, 5mM HEPES; pH 7.5 at 25°C) which contained 50μg ml^{-1} gentamycin and stored at 18°C.

KCNQ2 (in pCIN3 vector) and KCNQ3 (in pCIH6) were linearised and transcribed to RNA using T7 or T3 polymerase (Promega Wizard kit). m'G(5')pp(5')GTP capped cRNA was injected into oocytes (20-50nl of 1μgμl^{-1} RNA per oocyte) and whole-cell currents were recorded using two-microelectrode voltage-clamp (Geneclamp amplifier, Axon instruments Inc.) 3 to 5 days post-RNA injection. Microelectrodes had a resistance of 0.5 to 2MΩ when filled with 3M KCl. In all experiments oocytes were voltage-clamped at a holding potential of –90mV in ND96 solution (superfused at 2ml per min.) and test compounds were applied by addition to this extracellular solution. Current-voltage curves were constructed by applying 800ms voltage-clamp pulses from the holding potential of –90mV to test potentials between –85mV and +30mV. .

Whole-cell currents were recorded from oocytes expressing KCNQ2 alone, KCNQ3 alone and an equimolar combination of KCNQ2 plus KCNQ3. Mean current amplitude (at +20mV) was 152 +/- 21nA for KCNQ2 alone, 157 +/- 19nA for KCNQ3 alone and 1467 +/- 420nA for KCNQ2 & KCNQ3. Further characterisation of the KCNQ2/KCNQ3 heteromeric channel (current-voltage curve, conductance plot, linopirdine block) gave similar results to those reported in the literature (Yang, W.-P., Levesque, P.C., Little, W.A., Conder, M.L., Ramakrishnan, P., Neubauer, M.G. & Blanar, M.A, (1998) Functional expression of two KvLQT1-related potassium channels responsible for an inherited idiopathic epilepsy. *J. Biol. Chem.,* **31**: 19419-19423 and Wang, H.-S., Pan, Z., Shi, W., Brown, B.S.,. Wymore, R.S., Cohen, I.S., Dixon, J.E. & McKinnon, D (1998) KCNQ2 and KCNQ3 potassium channel subunits: molecular correlates of the M-channel. *Science* **282**: 1890-1893).

The effects of retigabine were studied in oocytes expressing equimolar KCNQ2 plus KCNQ3. Application of 10μM retigabine led to a pronounced 20mV hyperpolarising shift in the threshold for KCNQ current activation (n=5), such that an augmentation of KCNQ current was seen over the normal physiological range of membrane potentials. For example, at a test potential

of –60mV, outward KCNQ current amplitude increased 8-fold in the presence of retigabine (6.2-fold at –70mV; 7.1-fold at –50mV; n=5). These changes in KCNQ current amplitude were associated with an increase in the rate of current activation: Retigabine increased the rate of current activation 15-fold at a test potential of –40mV, and 3-fold at a test potential of –30mV (data fitted to a single exponential in each case).

Application of retigabine led to a marked alteration in the properties of the KCNQ2/3 tail currents. In these experiments the voltage clamp protocols comprised a 1s prepulse from –100mV to +40mV to fully activate the KCNQ2/3 channel, followed by a 6s pulse to test potentials between –30mV and –110mV. At the most positive test potentials (-30mV, -40mV) a steady state KCNQ2/3 tail current was recorded during the test pulse, suggesting that deactivation does not occur at these test potentials. With subsequent pulses to less positive membrane potentials (-50mV to –110mV) channel deactivation was observed but the rate was significantly slowed in comparison to control current data. These results suggest that in the presence of retigabine, the voltage dependence of channel deactivation shifts to more hyperpolarised membrane potentials.

Further experiments were carried out in oocytes held under current clamp. In these experiments the retigabine-induced shift in KCNQ activation curve led to a hyperpolarisation of the cell. The half maximal inhibitory concentration for this hyperpolarisation was 5.2μM (95% confidence limits 3.9-7.0μM) and the Hill slope was 1.1 ± 0.1.

In conclusion, we have shown that retigabine opens KCNQ2/3 potassium channels, apparently through an increase in the kinetics of channel activation. Since KCNQ2 and KCNQ3 are widely and prominently expressed throughout the central nervous system, the properties of retigabine on the KCNQ2/3 channel are likely to be a major contributor of its anti-convulsant action in vivo.

Expression of KCNQ2 in *Xenopus* oocytes: Modulation by Retigabine.

Using a specialist ooctye expression vector, pSP64t (Kreig PA and Melton DA (1984) Functional messenger RNAs are produced by SP6 in vitro translation

of cloned cDNAs. Nucleic Acids Research 12:7057-7070) we were able to successfully record currents from oocytes expressing KCNQ2 alone. Application of 10μM retigabine led to a pronounced 20mV hyperpolarising shift in the threshold for KCNQ2 current activation, increased KCNQ current amplitude over a range of test potentials (control = 145+/-34nA; retigabine = 501+/-116nA at –50mV, n=7) and increased the rate of current activation (mean delay at –40mV: control 132+/-16ms; retigabine 75+/-7ms). This data suggests that at least a part of retigabine's actions on the KCNQ2/3 heteromer occurs through an interaction with the KCNQ2 channel.

In addition to the anti-convulsant properties of retigabine where the drug protected against pentylene tetrazol-induced seizures in rats with an ED50 of 6.2 mg/kg (Loscher, W., Honack, D., Fassbender, C.P., & Nolting, B. (1991). The role of technical, biological and pharmacological factors in the laboratory evaluation of anticonvulsant drugs. III. Pentylenetetrazole seizure models. *Epilepsy Res.* **8**: 171-189), retigabine was also active in the carageenan model of inflammatory pain with an ED50 of 4.5 mg/kg (Clayton, N.M., Oaklety, I., Thompson, S., Wheeldon, A. Sargent, B. & Bountra, C. (1997). Validation of the dual weight averager as an instrument for the measurement of clinically relevant pain. *Br. J. Pharmacol.* 120: P78). Based on this result it is extremely likely that an opener of KCNQ2/3 will be active in pain.

Retigabine and pharmaceutically acceptable salts and solvates thereof may be prepared, formulated and administered according to the methods described in USP5,384,330, incorportaed herein by reference.

KCNQ2/3 potassium channel openers, including retigabine, may, for example, be formulated for oral, buccal, parenteral, depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose). Oral and parenteral formulations are preferred.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl

methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

KCNQ2/3 potassium channel openers may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

KCNQ2/3 potassium channel openers may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

KCNQ2/3 potassium channel openers may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, KCNQ2/3 potassium channel openers may be formulated as solutions for administration via a suitable metered or unit dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

Suitable dose ranges are described in the art, that is to say that for use in conditions according to the present invention the compounds may be used at doses appropriate for other conditions for which KCNQ2/3 compounds, including retigabine, are known to be useful. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient, and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected. A suitable dose range is for example 0.01 to 1000 mg/kg, such as from 0.1 to about 200 mg/kg, e.g. 0.1 mg/kg to 10 mg/kg, bodyweight per day.

The KCNQ2/3 potassium channel openers useful in the instant invention may, if desired, be administered in combination with one or more other therapeutic agents and formulated for administration by any convenient route in a conventional manner. Appropriate doses will be readily appreciated by those skilled in the art.

Claims

1. The use of a KCNQ2/3 potassium channel opener in the preparation of a medicament for use as an anti-epileptic.

2. The use of a KCNQ2/3 potassium channel opener in the preparation of a medicament for: use as a muscle relaxant, fever reducer, or anxiolytic; use in migraine, bipolar disorder, unipolar depression, functional bowel disorders, or tinnitus; use in preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence - inducing agent; use in cancerous diseases, inflammatory processes, or ophthalmic diseases; and use especially as an analgesic.

3. A method for the treatment of a mammal, including man, suffering from or susceptible to epilepsy, comprising administration of an effective amount of a KCNQ2/3 potassium channel opener.

4. A method: of producing a muscle relaxant, fever reducing, or anxiolytic effect; for treating migraine, bipolar disorder, unipolar depression, functional bowel disorders, or tinnitus; for preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence - inducing agent; for treating cancerous diseases, inflammatory processes, or ophthalmic diseases; and especially of producing an analgesic effect; in a mammal, including man, comprising administration of an effective amount of a KCNQ2/3 potassium channel opener.

5. The use of retigabine in the preparation of a medicament for the treatment of conditions ameliorated by KCNQ2/3 potassium channel opening.

6. The use of retigabine in the preparation of a medicament for: use in neurotransmission disorders; CNS disorders; functional bowel disorders; neurodegenerative diseases; neuroprotection; tinnitus; preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence - inducing agent; cancerous diseases; inflammatory processes;

ophthalmic diseases; cognitive disorders; and migraine; and use especially as a centrally acting analgesic.

7. A method for the treatment of a mammal, including man, suffering from or susceptible to conditions ameliorated by KCNQ2/3 potassium channel opening, comprising administration of an effective amount of retigabine.

8. A method for: the treatment of neurotransmission disorders, CNS disorders, functional bowel disorders, neurodegenerative diseases, or tinnitus; preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence - inducing agent; the treatment of cancerous diseases, inflammatory processes, ophthalmic diseases, cognitive disorders, or migraine; and producing a neuroprotecting, or more especially a centrally acting analgesic effect; in a mammal, including man, comprising administration of an effective amount of retigabine.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 January 2001 (11.01.2001)

PCT

(10) International Publication Number
WO 01/01970 A3

(51) International Patent Classification[7]: A61K 31/325, A61P 25/08

(21) International Application Number: PCT/GB00/02516

(22) International Filing Date: 30 June 2000 (30.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9915414.8 1 July 1999 (01.07.1999) GB

(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BURBIDGE, Stephen, Anthony** [GB/GB]; Glaxo Wellcome PLC, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **CLARE, Jeffrey, John** [GB/GB]; Glaxo Wellcome PLC, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **COX, Brian** [GB/GB]; Glaxo Wellcome PLC, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **DUPERE, Joseph** [GB/GB], 3 East Road, Whorley End, Cranfield, Bedfordshire MK43 0TD (GB). **HAGAN, Russell, Michael** [GB/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). **XIE, Xinmin** [GB/US]; 2633 Martinez Drive, Burlingame, Ca 94010 (US).

(74) Agent: **LANE, Graham**; GlaxoSmithKline, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG)

Published:
— *with international search report*

(88) Date of publication of the international search report:
28 February 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette

WO 01/01970 A3

(54) Title: NEW USES POTASSIUM CHANNEL OPENERS, SUCH AS THE TREATMENT OF EPILEPSY

(57) Abstract: The present invention relates to novel uses for retigabine and KCNQ2/3 potassium channel openers.

COMBINED DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY

ATTORNEY'S DOCKET
PG3733USW
First Names Inventor: Stephen Anthony BURBIDGE
Complete if known: App No.:
Filing Date
Group Art Unit:

( ) Declaration submitted with initial filing or

( )Declaration submitted after initial filing (surcharge required 37CFR1.16(e))

As below named inventor. I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

NEW USES FOR POTASSIUM CHANNEL OPENERS

the specification of which (check only one item below):

[ ]is attached hereto.
OR
[x] was filed on **30 June 2000** as United States application Serial No. _____ or **PCT** International

Application Number **PCT/GB00/02516** filed and was amended on (MM/DD/YYYY) _____(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I hereby claim foreign priority benefits under 35, U.S.C. §119 (a)-(d) or §365(b) of any foreign applications(s) for patent or inventor's certificate or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed:

PRIOR FOREIGN AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

Prior Foreign Application Number (s)	Country	Foreign Filing Date (MM/DD/YYYY))	PRIORITY CLAIMED
1 9915414.8	GB	July 1, 1999	X
2			
3.			
4.			
5.			

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below:

Application No.	Filing Date (MM/DD/YYYY)	
1.		
2.		
3.		
4.		

DECLARATION FOR "371" APPLICATION

COMBINED DECLARATION FOR UTILITY or DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY Continued

ATTORNEY'S DOCKET NUMBER: PG3733USW

I hereby claim the benefit under 35, U.S.C. §120 of any United States application or §365(c) of any PCT international application designating the United States of America that is listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. PARENT APPLICATION or PCT PARENT APPLICATION

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	STATUS (Check one) PATENTED	PENDING	ABANDONED

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the U.S Patent and Trademark Office connected therewith. (List name and registration number)

Send Correspondence to:	Direct Telephone Calls to:
	Bonnie Deppenbrock 919-483-1577

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

2	FULL NAME OF INVENTOR	FAMILY NAME: **BURBIDGE**	FIRST GIVEN NAME: **Stephen**	SECOND GIVEN NAME/INITIAL: **Anthony**
0	INVENTOR'S SIGNATURE	Signature X: Stephen Burbidge		Date: X 19.12.2001.
	RESIDENCE & CITIZENSHIP	CITY: **Stevenage**	STATE OR FOREIGN COUNTRY: **GB**	COUNTRY OF CITIZENSHIP: **GB**
1	POST OFFICE ADDRESS	POST OFFICE ADDRESS: **GlaxoSmithKline Five Moore Drive**	CITY: **Research Triangle Park**	STATE & ZIP CODE/COUNTRY: **North Carolina 27709, US** NC
2	FULL NAME OF INVENTOR	FAMILY NAME: **CLARE**	FIRST GIVEN NAME: **Jeffrey**	SECOND GIVEN NAME/INITIAL: **John**
0	INVENTOR'S SIGNATURE	Signature X		Date: X
	RESIDENCE & CITIZENSHIP	CITY: **Stevenage**	STATE OR FOREIGN COUNTRY: **GB**	COUNTRY OF CITIZENSHIP: **GB**
2	POST OFFICE ADDRESS	POST OFFICE ADDRESS: **GlaxoSmithKline Five Moore Drive**	CITY: **Research Triangle Park**	STATE & ZIP CODE/COUNTRY: **North Carolina 27709, US** NC
2	FULL NAME OF INVENTOR	FAMILY NAME: **COX**	FIRST GIVEN NAME: **Brian**	SECOND GIVEN NAME/INITIAL:
0	INVENTOR'S SIGNATURE	Signature X		Date: X
	RESIDENCE & CITIZENSHIP	CITY: **Stevenage**	STATE OR FOREIGN COUNTRY: **GB**	COUNTRY OF CITIZENSHIP: **GB**
3	POST OFFICE ADDRESS	POST OFFICE ADDRESS: **GlaxoSmithKline Five Moore Drive**	CITY: **Research Triangle Park**	STATE & ZIP CODE/COUNTRY: **North Carolina 27709, US** NC
2	FULL NAME OF INVENTOR	FAMILY NAME: **DUPERE**	FIRST GIVEN NAME: **Joseph**	SECOND GIVEN NAME/INITIAL:
0	INVENTOR'S SIGNATURE	Signature		Date: GB 3
	RESIDENCE & CITIZENSHIP	CITY: ~~Cranfield~~	STATE OR FOREIGN COUNTRY: **GB**	COUNTRY OF CITIZENSHIP: **GB**

DECLARATION FOR "371" APPLICATION

4	POST OFFICE ADDRESS	POST OFFICE ADDRESS **3 East Road** **Whorley End**	CITY **Cranfield**	STATE & ZIP CODE/COUNTRY **Bedfordshire MK43 0TD, GB**
2	FULL NAME OF INVENTOR	FAMILY NAME **HAGAN**	FIRST GIVEN NAME **Russell**	SECOND GIVEN NAME/INITIAL **Michael**
0	**INVENTOR'S SIGNATURE**	Signature X		Date: X 19th December 2001
0	RESIDENCE & CITIZENSHIP	CITY **Durham**	STATE OR FOREIGN COUNTRY **US**	COUNTRY OF CITIZENSHIP **GB**
5	POST OFFICE ADDRESS	POST OFFICE ADDRESS **GlaxoSmithKline** **Five Moore Drive**	CITY **Research Triangle Park**	STATE & ZIP CODE/COUNTRY **North Carolina 27709, US** NC
2	FULL NAME OF INVENTOR	FAMILY NAME **XIE**	FIRST GIVEN NAME **Xinmin**	SECOND GIVEN NAME/INITIAL
0	**INVENTOR'S SIGNATURE**	Signature		Date:
0	RESIDENCE & CITIZENSHIP	CITY **Burlingame**	STATE OR FOREIGN COUNTRY **US**	COUNTRY OF CITIZENSHIP **GB**
6	POST OFFICE ADDRESS	POST OFFICE ADDRESS **2633 Martinez Drive**	CITY **Burlingame**	STATE & ZIP CODE/COUNTRY **California 94010, US** CA

COMBINED DECLARATION FOR UTILITY or DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY Continued

ATTORNEY'S DOCKET NUMBER: PG3733USW

I hereby claim the benefit under 35, U.S.C. §120 of any United States application or §365(c) of any PCT international application designating the United States of America that is listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C F R §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. PARENT APPLICATION or PCT PARENT APPLICATION

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	STATUS (Check one) PATENTED	PENDING	ABANDONED

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the U.S Patent and Trademark Office connected therewith. (List name and registration number)

Send Correspondence to:	Direct Telephone Calls to:
	Bonnie Deppenbrock 919-483-1577

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

2	FULL NAME OF INVENTOR	FAMILY NAME: **BURBIDGE**	FIRST GIVEN NAME: **Stephen**	SECOND GIVEN NAME/INITIAL: **Anthony**
	INVENTOR'S SIGNATURE	Signature: X		Date: X
0	RESIDENCE & CITIZENSHIP	CITY: **Stevenage**	STATE OR FOREIGN COUNTRY: **GB**	COUNTRY OF CITIZENSHIP: **GB**
1	POST OFFICE ADDRESS	POST OFFICE ADDRESS: **GlaxoSmithKline Five Moore Drive**	CITY: **Research Triangle Park**	STATE & ZIP CODE/COUNTRY: **North Carolina 27709, US**
2	FULL NAME OF INVENTOR	FAMILY NAME: **CLARE**	FIRST GIVEN NAME: **Jeffrey**	SECOND GIVEN NAME/INITIAL: **John**
	INVENTOR'S SIGNATURE	Signature: X		Date: X 19/12/01
0	RESIDENCE & CITIZENSHIP	CITY: **Stevenage**	STATE OR FOREIGN COUNTRY: **GB**	COUNTRY OF CITIZENSHIP: **GB**
2	POST OFFICE ADDRESS	POST OFFICE ADDRESS: **GlaxoSmithKline Five Moore Drive**	CITY: **Research Triangle Park**	STATE & ZIP CODE/COUNTRY: **North Carolina 27709, US**
2	FULL NAME OF INVENTOR	FAMILY NAME: **COX**	FIRST GIVEN NAME: **Brian**	SECOND GIVEN NAME/INITIAL:
	INVENTOR'S SIGNATURE	Signature: X		Date. X
0	RESIDENCE & CITIZENSHIP	CITY: **Stevenage**	STATE OR FOREIGN COUNTRY: **GB**	COUNTRY OF CITIZENSHIP: **GB**
3	POST OFFICE ADDRESS	POST OFFICE ADDRESS: **GlaxoSmithKline Five Moore Drive**	CITY: **Research Triangle Park**	STATE & ZIP CODE/COUNTRY: **North Carolina 27709, US**
2	FULL NAME OF INVENTOR	FAMILY NAME: **DUPERE**	FIRST GIVEN NAME: **Joseph**	SECOND GIVEN NAME/INITIAL:
	INVENTOR'S SIGNATURE	Signature:		Date:
0	RESIDENCE & CITIZENSHIP	CITY: **Cranfield**	STATE OR FOREIGN COUNTRY: **GB**	COUNTRY OF CITIZENSHIP: **GB**

COMBINED DECLARATION FOR UTILITY or DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY Continued

ATTORNEY'S DOCKET NUMBER: PG3733USW

I hereby claim the benefit under 35, U.S.C. §120 of any United States application or §365(c) of any PCT international application designating the United States of America that is listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. PARENT APPLICATION or PCT PARENT APPLICATION

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	STATUS (Check one) PATENTED	PENDING	ABANDONED

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the U.S. Patent and Trademark Office connected therewith. (List name and registration number)

Send Correspondence to:	Direct Telephone Calls to:
	Bonnie Deppenbrock 919-483-1577

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

2	FULL NAME OF INVENTOR	FAMILY NAME: **BURBIDGE**	FIRST GIVEN NAME: **Stephen**	SECOND GIVEN NAME/INITIAL: **Anthony**
	INVENTOR'S SIGNATURE	Signature: X		Date: X
0	RESIDENCE & CITIZENSHIP	CITY: **Stevenage**	STATE OR FOREIGN COUNTRY: **GB**	COUNTRY OF CITIZENSHIP: **GB**
1	POST OFFICE ADDRESS	POST OFFICE ADDRESS: **GlaxoSmithKline Five Moore Drive**	CITY: **Research Triangle Park**	STATE & ZIP CODE/COUNTRY: **North Carolina 27709, US**
2	FULL NAME OF INVENTOR	FAMILY NAME: **CLARE**	FIRST GIVEN NAME: **Jeffrey**	SECOND GIVEN NAME/INITIAL: **John**
	INVENTOR'S SIGNATURE	Signature: X		Date: X
0	RESIDENCE & CITIZENSHIP	CITY: **Stevenage**	STATE OR FOREIGN COUNTRY: **GB**	COUNTRY OF CITIZENSHIP: **GB**
2	POST OFFICE ADDRESS	POST OFFICE ADDRESS: **GlaxoSmithKline Five Moore Drive**	CITY: **Research Triangle Park**	STATE & ZIP CODE/COUNTRY: **North Carolina 27709, US**
2	FULL NAME OF INVENTOR	FAMILY NAME: **COX**	FIRST GIVEN NAME: **Brian**	SECOND GIVEN NAME/INITIAL:
	INVENTOR'S SIGNATURE	Signature: X		Date: X 19th December 2001
0	RESIDENCE & CITIZENSHIP	CITY: **Stevenage**	STATE OR FOREIGN COUNTRY: **GB**	COUNTRY OF CITIZENSHIP: **GB**
3	POST OFFICE ADDRESS	POST OFFICE ADDRESS: **GlaxoSmithKline Five Moore Drive**	CITY: **Research Triangle Park**	STATE & ZIP CODE/COUNTRY: **North Carolina 27709, US**
2	FULL NAME OF INVENTOR	FAMILY NAME: **DUPERE**	FIRST GIVEN NAME: **Joseph**	SECOND GIVEN NAME/INITIAL:
	INVENTOR'S SIGNATURE	Signature:		Date:
0	RESIDENCE & CITIZENSHIP	CITY: **Cranfield**	STATE OR FOREIGN COUNTRY: **GB**	COUNTRY OF CITIZENSHIP: **GB**

DECLARATION FOR "371" APPLICATION

2	FULL NAME OF INVENTOR	FAMILY NAME **HAGAN**	FIRST GIVEN NAME **Russell**	SECOND GIVEN NAME/INITIAL **Michael**
	INVENTOR'S SIGNATURE	Signature		Date:
0	RESIDENCE & CITIZENSHIP	CITY **Durham**	STATE OR FOREIGN COUNTRY **US**	COUNTRY OF CITIZENSHIP **GB**
5	POST OFFICE ADDRESS	POST OFFICE ADDRESS **GlaxoSmithKline** **Five Moore Drive**	CITY **Research Triangle Park**	STATE & ZIP CODE/COUNTRY **North Carolina 27709, US**
2	FULL NAME OF INVENTOR	FAMILY NAME **XIE**	FIRST GIVEN NAME **Xinmin**	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE	Signature Xinmin Xie		Date: 15/1/2002
0	RESIDENCE & CITIZENSHIP	CITY **Burlingame**	STATE OR FOREIGN COUNTRY **US**	COUNTRY OF CITIZENSHIP **GB**
6	POST OFFICE ADDRESS	POST OFFICE ADDRESS **2633 Martinez Drive**	CITY **Burlingame**	STATE & ZIP CODE/COUNTRY **California 94010, US**

COMBINED DECLARATION FOR UTILITY or DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY Continued

ATTORNEY'S DOCKET NUMBER: PG3733USW

I hereby claim the benefit under 35, U.S.C §120 of any United States application or §365(c) of any PCT international application designating the United States of America that is listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. PARENT APPLICATION or PCT PARENT APPLICATION

U S Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	STATUS (Check one) PATENTED	PENDING	ABANDONED

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the U.S. Patent and Trademark Office connected therewith (List name and registration number)

Send Correspondence to: 23347 PATENT TRADEMARK OFFICE

Direct Telephone Calls to: Bonnie Deppenbrock 919-483-1577

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

2	FULL NAME OF INVENTOR	FAMILY NAME: **BURBIDGE**	FIRST GIVEN NAME: **Stephen**	SECOND GIVEN NAME/INITIAL: **Anthony**
	INVENTOR'S SIGNATURE	Signature		Date:
0	RESIDENCE & CITIZENSHIP	CITY: **Stevenage**	STATE OR FOREIGN COUNTRY: **GB**	COUNTRY OF CITIZENSHIP: **GB**
1	POST OFFICE ADDRESS	POST OFFICE ADDRESS: **GlaxoSmithKline Five Moore Drive**	CITY: **Research Triangle Park**	STATE & ZIP CODE/COUNTRY: **North Carolina 27709, US**
2	FULL NAME OF INVENTOR	FAMILY NAME: **CLARE**	FIRST GIVEN NAME: **Jeffrey**	SECOND GIVEN NAME/INITIAL: **John**
	INVENTOR'S SIGNATURE	Signature		Date:
0	RESIDENCE & CITIZENSHIP	CITY: **Stevenage**	STATE OR FOREIGN COUNTRY: **GB**	COUNTRY OF CITIZENSHIP: **GB**
2	POST OFFICE ADDRESS	POST OFFICE ADDRESS: **GlaxoSmithKline Five Moore Drive**	CITY: **Research Triangle Park**	STATE & ZIP CODE/COUNTRY: **North Carolina 27709, US**
2	FULL NAME OF INVENTOR	FAMILY NAME: **COX**	FIRST GIVEN NAME: **Brian**	SECOND GIVEN NAME/INITIAL:
	INVENTOR'S SIGNATURE	Signature		Date:
0	RESIDENCE & CITIZENSHIP	CITY: **Stevenage**	STATE OR FOREIGN COUNTRY: **GB**	COUNTRY OF CITIZENSHIP: **GB**
3	POST OFFICE ADDRESS	POST OFFICE ADDRESS: **GlaxoSmithKline Five Moore Drive**	CITY: **Research Triangle Park**	STATE & ZIP CODE/COUNTRY: **North Carolina 27709, US**
2	FULL NAME OF INVENTOR	FAMILY NAME: **DUPERE**	FIRST GIVEN NAME: ~~Joseph~~ Jonathan JEBD	SECOND GIVEN NAME/INITIAL:
	INVENTOR'S SIGNATURE	Signature X J - Dy		Date: X 13 March 2002
0	RESIDENCE & CITIZENSHIP	CITY: **Greenwich**	STATE OR FOREIGN COUNTRY: **GB**	COUNTRY OF CITIZENSHIP: **GB**
4	POST OFFICE ADDRESS	POST OFFICE ADDRESS: **17 Guildford Grove**	CITY: **Greenwich**	STATE & ZIP CODE/COUNTRY: **SE10 8JY, GB**